Amendments to the Specification:

Please amend the specification as follows:

Please delete the paragraph on page 8, lines 9-28 and replace it with the following paragraph:

For the heterologous production, a peptide such as a signal sequence and/or an affinity tag is operably fused to the N- terminus or to the C- terminus of the Nogo-A protein. Affinity tags such as the Strep-Tag® or the Strep-tag® II (Schmidt et al., supra) or oligohistidine tags (e.g., His_5- or His_6-tags) **(SEQ ID NOS 23-24, respectively in order of appearance)** or proteins such as glutathione-S- transferase which can be used for purification by affinity chromatography and/or for detection (e.g. using the specific affinity of the Strep-tag® for streptavidin) are examples of preferred fusion partners. Further examples of fusion partners which can be advantageous in practice are binding domains such as the albumin-binding domain of protein G. the immunoglobulin-binding domains of protein A or oligomerizing domains, if, for example, an avidity effect is desired. As indicated, the term fusion protein as used herein also includes truncated Nogo-A polypeptides that are equipped with a signal sequence. Signal sequences at the N terminus of a polypeptide according to the invention can be suitable to direct the polypeptide to a specific cell compartment during its biosynthesis, for example into the periplasm of *E. coli* or to the lumen of the endoplasmic reticulum of the eukaryotic cell or into the medium surrounding the cell. In doing so, the signal sequence is usually cleaved by a signal peptidase. It is also possible to use other targeting or signalling sequences which may also be located at the N-terminus of the polypeptide and which allow the localization thereof in specific cell compartments. A preferred signal sequence for secretion into the periplasm of *E. coli* is the OmpA signal sequence. A large number of further signal sequences is known in the art.

Please delete the paragraph on page 15, lines 19-22 and replace it with the following paragraph:

Figure 2 shows structural and functional characteristics of engineered IN-1 F_{ab} fragments as examples for binding molecules obtained by the method of the invention for identifying a compound having detectable and improved affinity to a Nogo-A protein; **IN-1, A32F, I.2.6, I.2.6(^{L96}V) and II.1.8 sequences disclosed as SEQ ID NOS: 19-22 and 12, respectively.**

Please delete the paragraph on page 15, lines 35-36 and replace it with the following paragraph:

Figure 6 shows the amino acid sequences of the full length Nogo-A protein of rat and human origin using the standard one letter code; **Figure 6A discloses SEQ ID NO: 1 and Figure 6B discloses SEQ ID NO: 2.**

Please delete the paragraph on page 16, lines 3-17 and replace it with the following paragraph:

Fig. 1A schematically shows the structural characteristics of the native neurite growth inhibitor Nogo-A and of examples of recombinant soluble truncated fragments derived from it in the present invention. The fragment NI-Fr1 consists of the amino acids 174 to 940 of the full length Nogo-A rat protein with the Strep-Tag® fused to its C-terminus. The fragment NI-Fr2 consists of the amino acids 223 to 940 of the full length Nogo-A rat protein with the Strep-Tag® fused to its C-terminus. The fragment Ni-Fr4 consists of amino acid 223 to 940 of the full length Nogo- A rat protein equipped with the Strep-Tag® at its N-terminus and a hexa-histidine-tag (His_6) **(SEQ ID NO: 24)** at its C-terminus. **Fig.1B** shows a SDS-PAGE analysis of the bacterially produced truncated fragment NI-Fr4. The periplasmic protein extract from *E. coli* JM83 harbouring pASK111-NIFr4 was loaded in lane 1. The flow-through of an IMAC column is shown in lane 2, eluted protein from IMAC column as applied to the streptavidin column in lane 3, flow-through of streptavidin column in lane 4, purified protein after streptavidin affinity chromatography in lane 5. Molecular sizes are indicated at the left. The proteins were visualized by staining with Coomassie Brilliant Blue.

Please delete the paragraph on page 19, lines 1-12 and replace it with the following paragraph:

The C-terminal *Strep*-tag encoded on pASK111-NiFr2 was exchanged by a His_6 **(SEQ ID NO: 24)** affinity tag by site-directed mutagenesis with the oligodeoxynucleotide 5'-CAC TTC ACA GGT CAA GCT TAT TAA TGG TGA TGG TGA TGG TGA GCG CTT TTA ACT ATG CTG CCC-3' (SEQ ID NO: 6). A *Kas*I restriction site was concomitantly introduced at the 5'-end of the cloned Nogo-A structural gene using the oligodeoxynucleotide 5'-GGT ATC CAT GTT CTT TAA AAG AGG CGC CCT GCG CTA CGG TAG C-3' (the *Kas*I recognition site is underlined) (SEQ ID NO: 7), resulting in the vector pASK111-NiFr3. The region encoding the Nogo-A fragment together with the His_6 tag **(SEQ ID NO: 24)** was finally subcloned via *Kas*I and *Nsi*I (cutting within the vector, downstream of the Cam^r gene) on pASK- IBA4 (Skerra and Schmidt, (2000) *Methods Enzymol.*, **326A**, 271-304), which provided the sequence for an N-terminal *Strep*-tag II directly downstream of the OmpA signal sequence. The resulting vector was dubbed pASK111-NiFr4 (SEQ ID NO: 15).

Please delete the paragraph on page 20, lines 15-27 and replace it with the following paragraph:

All Nogo-A fragments (NI-Fr1 (SEQ ID NO: 16), NI-Fr2 (SEQ ID NO: 17)) of the rat protein as well as corresponding human polypeptides) were purified from the periplasmic protein extract via the *Strep*-tag fused to their C-termini employing streptavidin affinity chromatography (Skerra and Schmidt, supra), whereby elusion was effected under mild conditions in the presence of desthiobiotin. After dialysis against chromatography buffer (50 mM NaP_i, pH 7.5, 150 mM NaC1, 1 mM EDTA) and concentration (Vivaspin 15, MWCO 30 kDa; Greiner, Frickenhausen, Germany) of the eluate further purification was achieved by gel filtration on a Superdex 200 prep grade column (Pharmacia, Uppsala, Sweden) using Dynamax SD-300 HPLC equipment (Rainin, Woburn, MA). NI-Fr4 (SEQ ID NO: 18) was first purified by means of the His_6 tag **(SEQ ID NO: 24)** via IMAC (Skerra, *Gene*, **141**,

(1994a) 79-84) using 50 mM NaPi, pH 7.5, 1 M NaC1 as chromatography buffer and a linear elusion gradient from 0 to 75 mM imidazole•HCl. The specifically eluted protein fraction was then subjected to streptavidin affinity chromatography as above.

Please delete the paragraph on page 22, lines 1-13 and replace it with the following paragraph:

The wild-type NI-Fr2 (SEQ ID NO: 17) protein still gave rise to certain truncated products, which was considered undesirable for precise binding measurements (see below). Therefore, a doubly tagged version of the recombinant protein was prepared using an otherwise identical expression system. First, the *Strep*-tag at the C-terminus was exchanged by a His_6-tag **(SEQ ID NO: 24)** (yielding NI-Fr3 as an intermediate construct, not shown), and, second, the *Strep*-tag was inserted at the N-terminus again, downstream of the OmpA signal peptide. Interestingly, the yield of bacterially produced soluble protein, termed NI-Fr4 (SEQ ID NO: 18) (cf. **Fig.lA**), was found to be significantly higher (by a factor of 2.5, approaching 300 $\mu g\ L^{-1}\ OD^{-1}$). NI-Fr4 (SEQ ID NO: 18) was isolated from the periplasmic protein fraction in two steps by immobilized metal affinity chromatography (IMAC) followed by streptavidin affinity chromatography as described above. This protein was essentially pure, just a minor fraction of truncated polypeptide chains was still detectable (**Fig.1B**).

Please delete the paragraph on page 23, lines 2-17 and replace it with the following paragraph:

The IN-1 F_{ab} fragment and its mutants were produced utilizing the vectors pASK88, pASK106 or pASK107. All of them encode a chimeric F_{ab} fragment with variable domains derived from the mouse monoclonal antibody IN-1 and human constant domains belonging to the subclass IgG1/κ(see above). Secretion into the oxidizing milieu of the bacterial periplasm is ensured by the presence of signal peptides at the N-termini of both chains (Skerra, 1994a, supra) and transcription of the artificial dicistronic operon is under tight control of the chemically inducible *tet*$P/^O$ (Skerra, *Gene*, (1994b) **151**, 131-135). pASK88 (SchTweck and

Skerra, supra) was used for soluble expression and purification via the His_6 tag **(SEQ ID NO: 24)** attached to the C- terminus of the heavy chain (Fiedler and Skerra, (2001a) In Kontermann, R. and Dübel, S. (eds.), Antibody Engineering. Springer Verlag, Heidelberg, pp. 243-256; Skerra, 1994b), whereas pASK107 provided the *Strep*-tag II for streptavidin affinity purification instead. pASK106 codes for a F_{ab} fragment similarly as pASK88 but with an albumin-binding domain (ABD) appended to the C- terminus of the light chain (König and Skerra, (1998) *J. Immunol. Methods*, **218**, 73-83). The variable domain genes were exchanged between the differing vector formats using conserved restriction sites as described (Skerra, 1994a).

Please delete the paragraph on page 24, lines 18-33 and replace it with the following paragraph:

The recombinant IN-1 F_{ab} fragments were purified either by IMAC via the His_6 tag **(SEQ ID NO: 24)** fused to the C-terminus of their heavy chain (Fiedler and Skerra, 2001a, supra) or, when using pASK107 (cf. above), via streptavidin affinity chromatography (Schlapschy and Skerra, (2001) In Kontermann, R. and Dübel, S. (eds.) Antibody Engineering. Springer Verlag, Heidelberg, pp. 292-306). IMAC was also performed under FPLC conditions using a POROS MC/M column (0.46 cm x 10 cm; PerSeptive Biosystems, Wiesbaden, Germany) charged with Zn^{2+} ions and Dynamax SD-300 HPLC equipment (Rainin, Woburn, MA) operating at a flow rate of 2.0 ml/min. 12.5 ml of periplasmic extract from a 2 **L** *E. coli* culture dialyzed against 50 mM NaP_i, pH 7.5, 500 mM betaine was applied to the column and, after washing with dialysis buffer, elusion was effected by application of a linear gradient of 200 mM imidazole•HCl, pH 7.5, 50 mM NaP_i, 500 mM betaine against dialysis buffer. This method enabled a five-fold quicker purification compared with the conventional procedure of Fiedler and Skerra, 2001a, supra, yielding recombinant F_{ab} fragments with an apparent purity of >95 % as estimated from SDS-PAGE. The yields of purified recombinant proteins from 2 L shaker-flask experiments were highly reproducible

and varied between 0.04 and 0.8 mg L^{-1} OD^{-1} for the different F_{ab} fragments.

Please delete the paragraph on page 28, lines 8-14 and replace it with the following paragraph:

For soluble production of the recombinant F_{ab} fragments in a standard format (i.e. without the ABD domain but still having a His_6 tag **(SEQ ID NO: 24)** fused to the C-terminus of the heavy chain) the mutagenized V_L gene cassettes from seven selected clones (cf. Table I) were subcloned on pASK88-IN1 (Fiedler and Skerra, (1999) *Protein Expr. Purif.*, **17**, 421-427). The mutants were produced in shaker flask cultures and isolated from the periplasmic protein fraction in one step via IMAC. All F_{ab} fragments contained the light and heavy chains in stoichiometric composition and quantitatively linked via a disulphide bond.

Please delete the paragraph on page 30, lines 24-26 and replace it with the following paragraph:

For each measurement the derivatized chip surface was charged with 70 µl 0.5 mM $NiSO_4$, followed by immobilization of NI-Fr4 via its His_6 tag **(SEQ ID NO: 24)** in one of the two flow channels by applying 70 µl of a 50 µg/ml solution of the purified recombinant protein.

Please delete the paragraph on page 31, lines 11-19 and replace it with the following paragraph:

By this way binding isotherms were obtained for the wild-type and engineered F_{ab} fragments (**Fig.3B**), from which dissociation constants were deduced. The K_D value for the recombinant wild-type IN-1 F_{ab} fragment was 7.8 ± 1.9 µM. In contrast, the dissociation constant for its II.1.8 mutant was 1.04 ± 0.18 µM, i.e. 8-fold better. Control experiments with

an unrelated protein, recombinant cystatin carrying a His_6-tag **(SEQ ID NO: 24)**, that was used instead of the Nogo-A fragment for coating of the sensor chip confirmed absence of unspecific binding (not shown).

Please delete the paragraph on page 31, lines 24-34 and replace it with the following paragraph:

For this purpose, cryosections (12 µm) of rat brain (Rattus norvegicus) were fixed for 10 minutes using ice-cold ethanol. The following incubation steps were then each performed for 1 h at room temperature in a humid chamber using PBS. Unless otherwise stated slides were washed for min with PBS. After blocking with 4 % (w/v) BSA the F_{ab} fragment (produced using the pASK88 vector type and purified via the His_6 tag **(SEQ ID NO: 24)**) was applied at a concentration of 100 µg/ml. After three washing steps bound F_{ab} fragment was detected with an anti-human Ck antibody alkaline phosphatase conjugate (Sigma), diluted 1:100. The sections were then washed three times with TBS (25 mM Tris/HCl, pH 7.4, 145 mM NaCl, 3 mM KC1) and staining was performed using a "Fast Red" kit (Roche Diagnostics). The microscopic slides were photographed on an Axiophot microscope (Carl Zeiss, Jena, Germany) using 10- or 20-fold magnification.